Original Research Article

# Development and evaluation of chitosan based oral controlled matrix tablets of losartan potassium

**Tallapaneni Vishnuvardhan Rao, GB Kiran Kumar, Mohammed Gulzar Ahmed, Vedamurthy Joshi**

*Department of pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B.G. Nagara, Nagamangala, Mandya, Karnataka, India*

## Abstract

**Aim and Background:** The novelty of the present study was to control the release profile of matrix tablets of losartan potassium prepared by using different concentrations of chitosan and trisodium citrate as cross-linking agent with combination of various release retardant polymers. **Materials and Methods:** Twelve formulations were prepared using HPMC K100M, carbopol 934P, and xanthan gum as polymers. Matrix tablets were prepared by wet granulation technique. The granules were subjected to precompression parameters such as angle of repose, loose bulk density, tapped bulk density, compressibility index. Tablets were evaluated for weight variation, hardness, drug content, *in-vitro* dissolution, stability studies, respectively. Drug -polymer compatibility studies were determined by FTIR spectroscopy. Further stability studies were carried out for 3months in accelerated conditions at 40°C and 75%RH. The granules of all formulations exhibited good flow and compressibility. *In-vitro* dissolution studies were carried out for 24 h using 0.1 N HCl for the first 2 h and pH 6.8 phosphate buffers for the remaining 22h. **Results:** It was found that among the 12 formulations F11 and F12 showed good dissolution profile to control the drug release. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer, first-order, and zero-order to evaluate the kinetics and the drug release. The drug release follows zero-order kinetics and the mechanism was found to be diffusion controlled and Case II transport. FT-IR spectroscopic studies revealed no interaction between drug and polymer. The stability studies indicated that F11 and F12 formulations were stable for 3months. **Conclusion:** The above results concluded that by combining different classes of polymers an acceptable release profile can be obtained in the fluctuating *in vivo* environment.

**Key words:** Chitosan, controlled release matrix tablets, losartan potassium, trisodium citrate

## INTRODUCTION

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. In conventional oral dosage forms drug dosage must be taken several times, which results in fluctuating drug levels in plasma. This drawback of conventional dosage form can be overcome by formulation of controlled release dosage forms, which provides drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with release profiles controlled by the special technological construction and design of the system. The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable, and topical use and inserts for placement in body cavities. Controlled release also denotes systems, which can provide some control whether this be of a temporal or spatial nature or both for drug release in the body.[1] The system attempts to control drug concentrations in the target tissues or cells.[2] Matrix systems offer several advantages relative to other extended release dosage forms like easy to manufacture, versatile, effective, low cost, and can be made to release high molecular weight compounds.[3] Since the drug is dispersed in the matrix system, accidental leakage of the total drug components is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release. Hypertension is one of the chronic disorders affecting a large number of populations in the world. Hypertension often is defined as a diastolic pressure of more than 90 mmHg because at this value the frequency of complication due to hypertension rises significantly.[4] Hypertension may also refer to increase the blood pressure in any blood vessel, such as pulmonary or portal hypertension.[5] It usually refers systolic arterial blood pressure.

**Address for correspondence:**
Asso. prof. G. B. Kiran Kumar,
Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B.G. Nagara, Nagamangala, Mandya, Karnataka, India.
E-mail: gbkk330@gmail.com

**Access this article online**

Quick Response Code:

Website: www.jpionline.org

DOI: 10.4103/2230-973X.104399

Systemic hypertension may leads to cerebrovascular accidents, myocardial infarction, congestive heart failure, and renal damage. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated.[6]

Losartan potassium is the first orally active angiotensin-II antagonist used in the treatment of hypertension either alone (or) in combination of hydrochlorothiazides. It is extensively metabolized in liver. It undergoes extensive biotransformation and has an elimination half life 1.5-2.5 h and hence it is suitable for oral controlled release.[3]

The current study aims at developing oral controlled release tablets of losartan potassium, using matrices HPMC K100M and carbopol 934P, xanthan gum with chitosan, and trisodium citrate as a cross-linking agent. The developed formulations were evaluated for weight variation, hardness, friability, and *in vitro* release studies.

## MATERIALS AND METHODS

Losartan potassium was obtained as gift sample from Divis Laboratories, India. HPMC K100M, carbopol 934, chitosan were obtained from HiMedia Laboratories Pvt. Ltd, Mumbai, India. Xanthan gum, trisodium citrate, di-basic calcium phosphate, magnesium stearate were procured S.D. Fine Chem. Ltd, Mumbai, India.

### Preparation of compressed matrices

Table 1 enlists the composition of different formulations prepared using varying amounts of the polymers (i.e., Carbopol 934P and HPMC K100M, xanthan gum, chitosan, trisodium citrate) and dicalcium phosphate as the diluent, along with the fixed quantity of magnesium stearate as lubricant. Drug and the excipients were homogeneously blended and subsequently compressed into flat-faced tablets using multi-punch tablet compression machine (India).

### Compatibility testing of drug with polymer fourier transforms infra-red spectroscopy

Fourier transforms infra-red (FTIR) study was carried out to check compatibility of drug with polymers. The spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer (Thermo Nicolet 380, India).

### Evaluation of controlled release tablets[7,8]

The prepared controlled release tablets were evaluated for uniformity of weight using 20 tablets, hardness using 6 tablets (Monsanto hardness tester), and friability using 20 tablets (Roche Friabilator).

### Drug content

Five tablets were weighed and triturate, from that transfer an accurately weighed portion of the powder equivalent to about 100 mg of losartan potassium in a 100 ml volumetric flask containing buffer solution and then concentration is measured at $\lambda_{max}$ 205 nm.

### *In-vitro* dissolution studies

The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8, maintained at 37 ± 0.5°C. An aliquot (5 ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer (Shimadzu-1700, Japan) at 205 nm. The study was performed in triplicate.

### Release kinetics[9]

*In-vitro* drug release data were analyzed as per zero order, first order, Higuchi equation models to assess the drug release kinetics and mechanism of release from the tablets.

### Stability studies[10]

The optimized formulation was subjected for 3 month stability study according to International Conference on Harmonization (ICH) guidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were then stored at 25°C/60% RH, 30°C/65% RH, 40°C/75% RH for 3 months and evaluated for their permeation study.

## RESULTS

Losartan potassium was dissolved in both pH 1.2 and pH 6.8, further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu UV"1700, Japan) in the range from 190 to 380 nm, using pH 1.2 and pH 6.8 as blank. The $\lambda_{max}$ of the drug was found to be 205 nm. As shown in Figure 1 the FTIR analysis of Losartan

**Table 1: Composition of losartan potassium control release matrix tablet (F1-F12)**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Losartan potassium | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| HPMCK100M | 100 | 100 | - | - | - | - | 50 | 50 | 50 | 50 | - | - |
| Carbopol934P | - | - | 100 | 100 | - | - | 50 | 50 | - | - | 50 | 50 |
| Xanthan gum | - | - | | | 100 | 100 | - | - | 50 | 50 | 50 | 50 |
| Chitosan | 10 | 20 | 10 | 20 | 10 | 20 | 10 | 20 | 10 | 20 | 10 | 20 |
| Trisodium citrate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Di calcium phosphate | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Total | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

*All the quantities are expressed as mg per tablet

potassium showed characteristic peaks at 3621/cm due to N–H stretching, 3211/cm due to Ar–OH stretching, 2956 due to Ar (H), at 1645 because of C-O stretching and 1377 due to C-N stretching. Moreover, we can observe that, as shown in Figures 2-4 the peaks at the same as above with slight variation was observed for the mixture of drug with different polymers like HPMC K 100 M, carbopol934P, xanthan gum, respectively. Hence, it was found that all the polymers used in formulations were compatible with Losartan potassium. Flow properties of the granules were evaluated by determining the bulk density 0.244 ± 0.124 to 0.427 ± 0.136, tapped density 0.275 ± 0.091 to 0.526 ± 0.116, angle of repose 16.43 ± 0.53 to 25.90 ± 0.45, and compressibility index 11.27 ± 0.092 to 24.37 ± 0.147 [Table 2]. The measured hardness of tablets of each batch ranged between 5.0 ± 0.05 kg/cm$^2$ and 5.7 ± 0.07 kg/cm$^2$ [Table 3] this ensures good handling characteristics of all batches. The values of friability test were tabulated in Table 3. The friability was in the range 0.312 ± 0.0036 to 0.996 ± 0.051. Hence, less than 1% in all formulations ensuring that the tablets were mechanically stable. The percentage weight variation was within pharmacopoeia limits of ±5% of weight. The weights variations range from199.5 ± 0.14 to 200.8 ± 1.6. Hence, all the tablets were found to be uniform with low standard deviation values [Table 3]. The percentage of drug content was found to be above 90% of losartan potassium, which was within acceptable limits. Table 3 shows the results of drug content uniformity in each batch. The

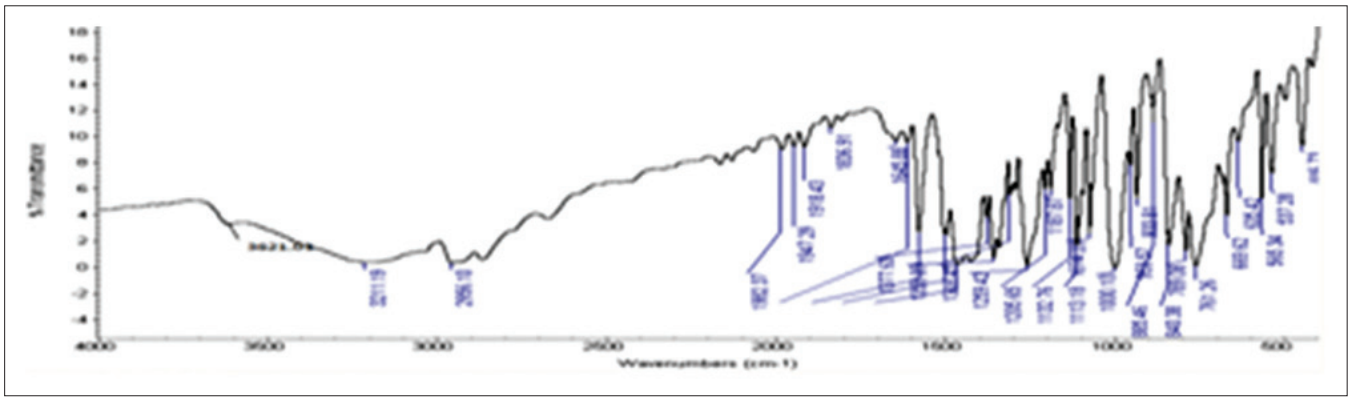

**Figure 1:** FT-IR spectra of losartan potassium

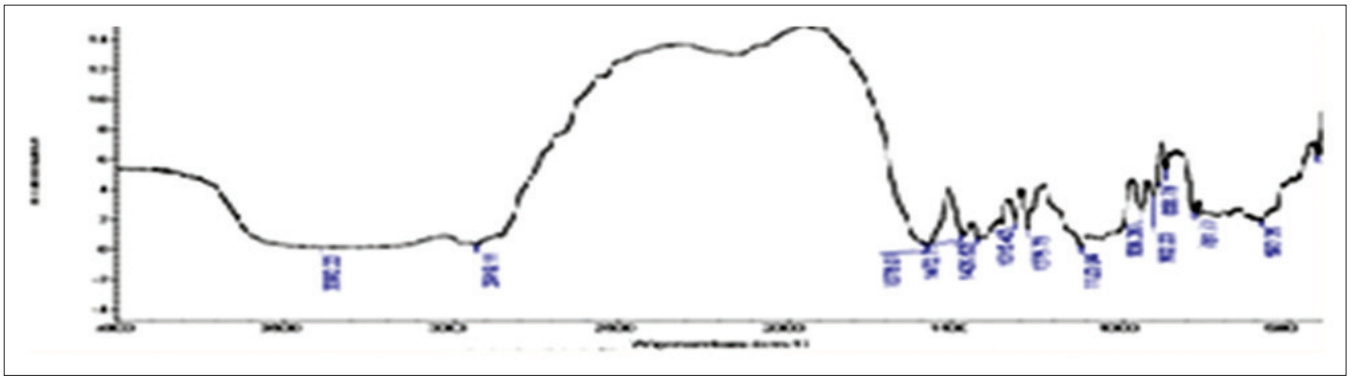

**Figure 2:** FT-IR spectra of losartan potassium with HPMCK100M

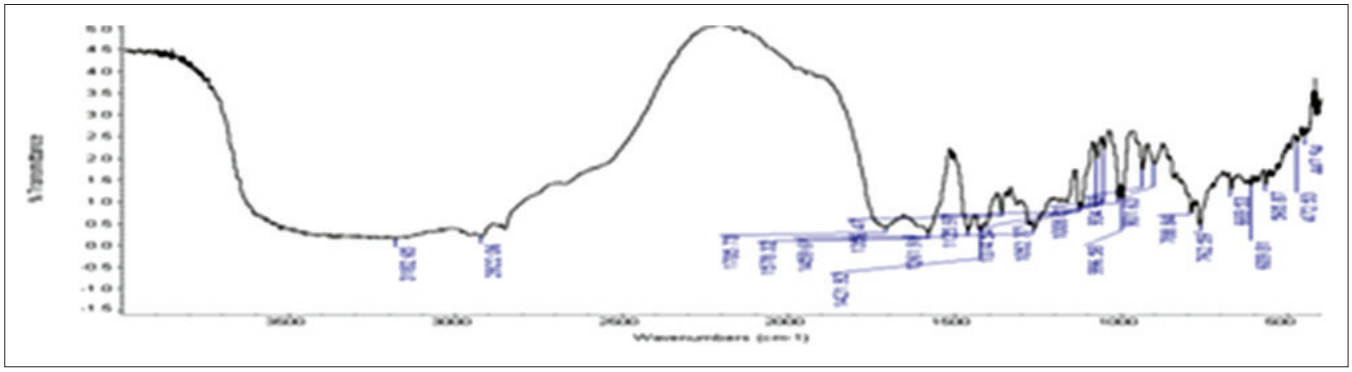

**Figure 3:** FT-IR spectra of losartan potassium with carbopol 934P

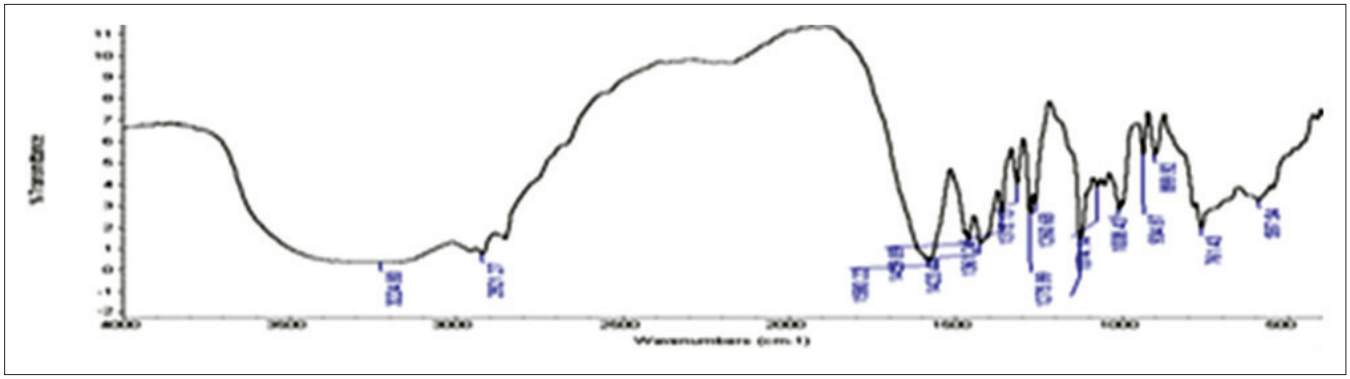

**Figure 4:** FT-IR spectra of losartan potassium with xanthan gum

**Table 2: Precompressional parameters of all formulations**

| Formulation | Bulk density G/CC | Tapped density G/CC | Compressibility index % | Angle of repose (θ) |
|---|---|---|---|---|
| F1 | 0.36±0.112 | 0.427±0.120 | 15.78±0.03 | 24.2±0.07 |
| F2 | 0.314±0.109 | 0.363±0.101 | 13.64±0.186 | 23.60±0.5 |
| F3 | 0.248±0.121 | 0.304±0.041 | 17.2±0.070 | 17.53±0.95 |
| F4 | 0.244±0.124 | 0.275±0.091 | 11.27±0.092 | 16.43±0.53 |
| F5 | 0.427±0.136 | 0.526±0.116 | 18.82±0.112 | 21.80±0.49 |
| F6 | 0.383±0.070 | 0.445±0.102 | 13.93±0.08 | 25.90±0.45 |
| F7 | 0.336±0.001 | 0.404±0.070 | 16.83±0.041 | 24.09±0.32 |
| F8 | 0.367±0.070 | 0.423±0.001 | 13.23±0.078 | 23.39±0.34 |
| F9 | 0.384±0.134 | 0.503±0.012 | 23.65±0.045 | 21.90±0.56 |
| F10 | 0.301±0.001 | 0.398±0.096 | 24.37±0.147 | 20.80±0.52 |
| F11 | 0.301±0.009 | 0.343±0.108 | 12.04±0.036 | 22.9±0.62 |
| F12 | 0.353±0.131 | 0.412±0.082 | 14.32±0.075 | 21.99±0.20 |

**Table 3: Post compressional parameters of all formulations**

| Formulation | Weight variation (mg) | Hardness (kg/cm²) | Friability (%) | Drug content (%) |
|---|---|---|---|---|
| F1 | 199.5±0.62 | 5.1±0.03 | 0.837±0.002 | 90.25±0.025 |
| F2 | 199.8±0.52 | 5.2±0.08 | 0.996±0.051 | 98.46±0.020 |
| F3 | 200.5±0.32 | 5.0±0.07 | 0.334±0.007 | 96.92±0.045 |
| F4 | 200.3±0.15 | 5.3±0.09 | 0.505±0.001 | 98.07±0.05 |
| F5 | 200.1±0.19 | 5.1±0.06 | 0.668±0.002 | 93.02±0.055 |
| F6 | 200.5±0.17 | 5.0±0.05 | 0.662±0.0025 | 94.57±0.015 |
| F7 | 199.5±0.56 | 5.2±0.08 | 0.843±0.004 | 92.64±0.098 |
| F8 | 200.1±0.51 | 5.4±0.06 | 0.714±0.004 | 92.77±0.056 |
| F9 | 199.7±0.48 | 5.2±0.07 | 0.698±0.0049 | 90.35±0.066 |
| F10 | 200.6±0.21 | 5.4±0.09 | 0.725±0.002 | 96.48±0.02 |
| F11 | 200.2±0.14 | 5.7±0.07 | 0.503±0.0021 | 95.97±0.036 |
| F12 | 200.8±0.21 | 5.2±0.08 | 0.312±0.0036 | 98.07±0.045 |

*in-vitro* drug release was studied with USP-II (Paddle type) dissolution apparatus in both stimulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8 phosphate buffer) for 24 h [Table 4].

## DISCUSSION

The present study reveals to control the drug release by increasing the concentration of chitosan as a cross-linking agent with different polymers like HPMC K100M, carbopol 934P, xanthan gum. The combination of different ratios of carbopol 934P and xanthan gum with chitosan (F11 and F12) showed better release profile 99.72% and 98.70%, respectively, rather than other combinations like HPMC K100M and carbopol 934P, HPMC K100M and xanthan gum [Figures 5-6]. The values of release rate exponent (*n*), calculated as per the algorithm proposed by Higuchi and Korsemeyer, ranged between 0.961 and 1.259. The drug release from matrix system follows zero-order kinetics and the mechanism was found to be diffusion controlled and Case II transport. The selected formulation F11 and F12 were subjected to accelerated stability studies for 90 days at 25°C/60% RH, 30°C/65% RH, 40°C/75% RH, *in vitro* permeation study was performed on every 30 days and showed negligible change in permeation profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content.

## CONCLUSION

The objective of the present was to investigate the possibility of controlling of losartan potassium release from matrix tablet prepared by different polymers. The preformulation studies were carried out, which ruled out the interaction between the drug and polymers. The granules were punched into tablet and evaluated by post compression parameter like weight variation, hardness, friability, and drug content. All formulation showed acceptable flow properties and with required hardness, weight

**Table 4: Drug release studies of F1 to F12**

| Formulation | 1 h | 2 h | 6 h | 10 h | 14 h | 18 h | 22 h | 24 h |
|---|---|---|---|---|---|---|---|---|
| F1 | 3.733±0.004 | 5.329±0.002 | 41.127±0.004 | 66.262±0.004 | 79.899±0.002 | 85.425±0.005 | 93.154±0.002 | 95.425±0.008 |
| F2 | 3.080±0.001 | 5.113±0.003 | 40.499±0.009 | 62.376±0.003 | 78.748±0.013 | 83.842±0.034 | 89.665±0.015 | 94.580±0.095 |
| F3 | 5.670±0.02 | 7.704±0.01 | 42.69±0.03 | 63.472±0.005 | 79.251±0.011 | 86.429±0.09 | 90.550±0.004 | 94.930±0.004 |
| F4 | 4.616±0.004 | 6.499±0.005 | 40.615±0.006 | 62.571±0.004 | 77.235±0.006 | 84.332±0.007 | 89.583±0.16 | 93.920±0.014 |
| F5 | 2.510±0.015 | 4.553±0.002 | 40.156±0.003 | 67.277±0.001 | 82.761±0.004 | 88.403±0.005 | 93.330±0.036 | 97.785±0.003 |
| F6 | 2.263±0.002 | 4.120±0.011 | 38.977±0.001 | 65.136±0.005 | 78.460±0.003 | 87.560±0.011 | 92.780±0.015 | 96.799±0.007 |
| F7 | 2.312±0.003 | 4.696±0.002 | 45.227±0.002 | 63.091±0.003 | 73.296±0.003 | 88.186±0.002 | 91.397±0.006 | 95.425±0.008 |
| F8 | 2.241±0.004 | 4.518±0.005 | 42.912±0.001 | 59.117±0.008 | 67.780±0.015 | 82.870±0.017 | 90.285±0.002 | 94.580±0.095 |
| F9 | 2.593±0.002 | 4.475±0.002 | 43.341±0.006 | 59.669±0.003 | 71.740±0.02 | 81.318±0.001 | 88.261±0.004 | 94.930±0.004 |
| F10 | 2.318±0.003 | 4.069±0.005 | 41.823±0.003 | 58.34±0.02 | 69.79±0.02 | 83.339±0.01 | 89.769±0.001 | 93.920±0.014 |
| F11 | 4.588±0.003 | 6.926±0.004 | 43.322±0.003 | 56.414±0.005 | 70.449±0.004 | 83.309±0.002 | 94.612±0.001 | 97.785±0.003 |
| F12 | 4.429±0.002 | 6.316±0.006 | 41.653±0.003 | 53.475±0.003 | 68.616±0.004 | 86.397±0.003 | 93.348±0.002 | 96.799±0.007 |

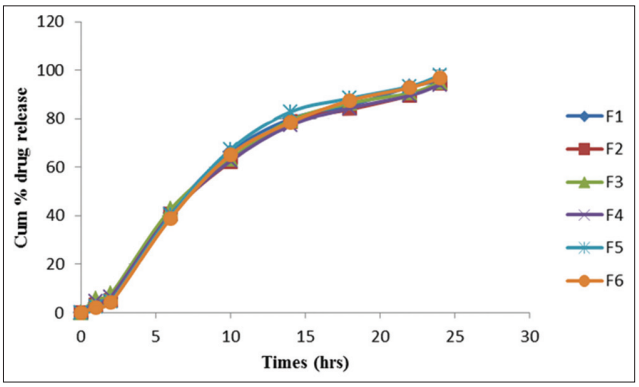


**Figure 5:** Cumulative percentage drug release Vs Time profile of formulation F1 to F6

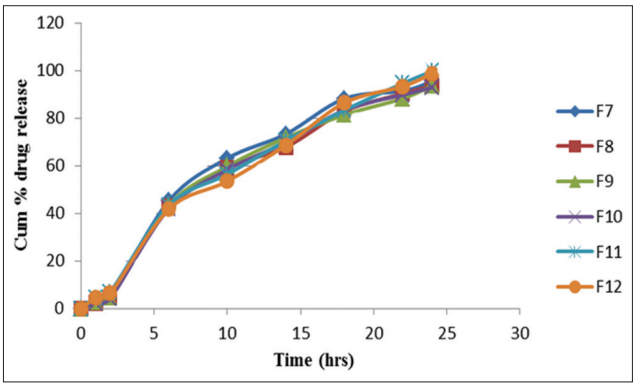


**Figure 6:** Cumulative percentage drug release Vs Time profile of formulation F7 to F12

variation, friability, and drug content. The *in-vitro* drug release was studies with USP XXII dissolution apparatus in both simulated gastric fluid and intestine fluid for a period of 24 h. The results of dissolution studies indicated that formulations F11 and F12 produced controlled effect with 99.72% and 98.70% of drug release over a period of 24 h than compared with other formulations. The mechanism of drug release was diffusion and case II transport. It can be concluded that the polymer plays a major role in the design of controlled release matrix tablet. The study reveals that the release of drug was low when the matrix tablet contained polymers with increasing concentration of chitosan as a cross-linking agent and also shows anomalous diffusion kinetics. Hence, it clearly manifests that, the necessity of combining different classes of polymers is required to to get an acceptable pharmacokinetic profile.

## ACKNOWLEDGMENTS

The authors are sincerely thankful to Sri Adichunchanagiri College of Pharmacy, B.G.Nagara for providing them the infrastructure facilities and moral support to carry out this research work.

## REFERENCES

1. Robinson JR, Lee HL. Controlled drug delivery: Fundamentals and applications. 2nd ed. New York: Marcel Dekker Inc.; 1987. p. 373.
2. Gennaro AR. Reminngton. The science and practice of pharmacy. 19th ed. Vol. 2. 1995. Hagers Town: Maryland, Mac Publishing Co; p. 1662.
3. Raju DB, Suresh John K, Varma MM. Formulation and evaluation of losartan potassium matrix tablets for oral controlled release. J Chem Pharm Res 2010;2:130-5.
4. Thomas W, Yip Lee In: Lee TW, Joseph RR. Remington's The Science and Practice of Pharmacy. 20th ed. Maryland: Lippincott Williams and Wilkins; 2000. p. 1069-70.
5. Health Encyclopedia - Diseases and Conditions the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of Hypertension. 1997 (updated 2000).
6. Richard AH, Pamela CC. Anti Hypertensives. 4th ed. Lippincott's illustrated reviews: Pharmacology. New Delhi: Wolters Kluwer; 2009. p. 215.
7. Leon L, Lieberman Herbert A. Pharmaceutical Dosage forms: Tablets. In: The Theory and practice of industrial pharmacy. 3rd ed. USA: Lea and Febiger; 1991. p. 293-345.
8. Subrahmanyam CV. Textbook of Physical Pharmaceutics. 2nd ed. Delhi: Vallaba Prakashan; 2003. p. 180-234.
9. Korsemeyer RW, Peppas NA, Rosemann TJ, Mansdrofs Z. Macromolecular and modelling aspects of swelling - controlled systems. In: Controlled Release Delivery systems. New York: Marcel Dekker; 1983. p. 77.
10. ICH Q1A (R2) Stability testing guidelines: Stability Testing of new drug substances and products. [online]. Available from: http://www.tga.health.gov.au/docs/pdf/euguide/inch/273699r2en.pdf. [Last cited on 2008 Nov 10].

**How to cite this article:** Rao TV, Kiran Kumar GB, Ahmed MG, Joshi V. Development and evaluation of chitosan based oral controlled matrix tablets of losartan potassium. Int J Pharma Investig 2012;2:157-61.
**Source of Support:** Nil. **Conflict of Interest:** None declared.